Date of Approval: February 27, 2014

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application Number 141-422

PACCAL VET-CA1

Paclitaxel for injection

Powder for Injection

Dog

PACCAL VET-CA1 is indicated for the treatment of:

Nonresectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy

Resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy

Sponsored by:

Oasmia Pharmaceutical AB

Tables of Contents

I. GENERAL INFORMATION

A. File Number

Application Number 141-422

B. Sponsor

Oasmia Pharmaceutical AB
Vallongatan 1
Uppsala, 75228
Sweden

Drug Labeler Code: 52818

US Agent:
Kristen Khanna, PhD, MBA
Animal Clinical Investigation, LLC
4926 Wisconsin Ave NW
Washington, DC 20016

C. Proprietary Name

PACCAL VET-CA1

D. Established Name

Paclitaxel for injection

E. Pharmacological Category

Anti-neoplastic

F. Dosage Form

Powder for Injection

G. Amount of Active Ingredient

60 mg per vial

H. How Supplied

PACCAL VET-CA1 is supplied as a 60 mg lyophilized powder in a 75 mL clear glass single use vial. The lyophilized powder is reconstituted with 60 mL of Lactated Ringer's Solution to make a 1 mg/mL paclitaxel solution.

I. Dispensing Status

Rx

J. Dosage Regimen

Administer PACCAL VET-CA1 at 150 mg/m^2 body surface area (BSA) intravenously over 15-30 minutes, once every three weeks for up to four doses. Dose reductions of 10 mg/m^2 or dose delays may be used to manage adverse reactions.

K. Route of Administration

Intravenous Injection

L. Species/Class

Dog

M. Indication

Paccal Vet-CA1 is indicated for the treatment of:

Nonresectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy

Resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy

II. EFFECTIVENESS

Conditional Dose: The conditional dose for the indications "for the treatment of nonresectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy" and "for the treatment of resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy" is 150 mg/m^2 body surface area (BSA) administered intravenously once every three weeks for up to four cycles. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional use.

A. Dosage Characterization:

A dose of 150 mg/m^2 BSA of paclitaxel administered intravenously (IV) over 15-30 minutes every three weeks (one cycle) for three cycles is based on two pilot studies. During the course of clinical development, the PACCAL VET-CA1 formulation of paclitaxel was also referred to as PACLICAL or PACLICAL VET.

1. Study Title: A Clinical Pilot Study to Examine the Safety of PACLICAL in Metastatic Solid Tumour in the Dog. Study Number OAS-0501-CA.

   A single group, single-center, open label, dose escalating clinical study in 32 dogs with multi-centric, solid tumors was conducted to assess safety and pharmacokinetics of paclitaxel. Treatment consisted of an intravenous infusion of paclitaxel over approximately 15-30 minutes every three weeks for three cycles, with some dogs receiving four or five cycles. A cycle was defined as an interval of 21 days. The starting dose level was 175 mg/m^2 BSA. Dose reductions or escalations in increments of 25-50 mg/m^2 were allowed based on

the dogs' tolerance of paclitaxel. The dose could also be omitted or delayed for up to seven days within a cycle.

Only the first dog to enter the study received the planned starting dose of 175 mg/m^2. The occurrence of severe adverse reactions at 175 mg/m^2 (severe neutropenia, severe leukopenia, fever, diarrhea, dehydration, and fatigue) resulted in dose reductions in the subsequent dogs with initial doses ranging from 100 mg/m^2 to 150 mg/m^2. Bone marrow suppression with leukopenia, neutropenia, and thrombocytopenia were the most common adverse reactions seen throughout the study. Neutropenia was the primary dose limiting toxicity, occurring four to seven days after paclitaxel administration. In most cases the neutrophil count was normal by the next treatment. Gastrointestinal adverse reactions such as mild to moderate vomiting and diarrhea were commonly reported. Other common adverse reactions included mild anorexia and fatigue. The dogs maintained a good quality-of-life rating throughout treatment, despite the number of serious adverse reactions and dose-limiting toxicities noted in the study. The study established 150 mg/m^2 as the maximum tolerated dose of paclitaxel.

2. Study Title: A Multi-Center Open Single Arm Phase III Study to Determine Efficacy and Safety of PACLICAL VET in Mast Cell Tumors, Grade II, III in Dog.

   A single group, multi-center, open label clinical study in 29 dogs with nonresectable grade II or III mast cell tumors was conducted. Paclitaxel was administered as an intravenous infusion of 150 mg/m^2 BSA over approximately 15-30 minutes every three weeks for three cycles (21 $\pm$ 7 days). Five of the 29 dogs received four cycles. Dose reductions of 10 mg/m^2 or dose delays were allowed for management of hematological or non-hematological toxicities. Doses of 130 mg/m^2 to 150 mg/m^2 were administered during the study, and half of the dogs had a 10 mg/m^2 dose reduction to manage toxicities.

   All dogs experienced adverse reactions and 19 dogs exhibited severe adverse reactions. The most common reported adverse reactions were leukopenia and neutropenia on days four and seven of each cycle. In most cases the leukocyte and neutrophil counts were normal at the beginning of the next cycle. The most common serious adverse reaction in this study was Veterinary Cooperative Oncology Group– common terminology criteria for adverse events (VCOG-CTCAE) grade 4 neutropenia. Other common adverse reactions included diarrhea, vomiting, thrombocytopenia, lethargy, anorexia, alopecia, increases in liver enzymes, and anemia. At study termination, there were no significant changes in hematological or clinical chemistry tests compared with baseline tests obtained prior to treatment. The study further supports 150 mg/m^2 as the maximum tolerated dose of paclitaxel

Conclusion: These two studies support a conditional dose of 150 mg/m^2 BSA of paclitaxel administered intravenously over 15-30 minutes every three weeks for three to four cycles, with dose reductions of 10 mg/m^2 or dose delays to manage adverse reactions.

B. Reasonable Expectation of Effectiveness

1. Mammary Carcinoma

Reasonable expectation of effectiveness for the treatment of nonresectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy is supported by clinical data from 10 dogs with advanced stage mammary carcinoma that received treatment with paclitaxel as an intravenous infusion once every three weeks.

a. Academic Study: Poirier, VJ et al., Efficacy and Toxicity of Paclitaxel (Taxol) for the Treatment of Canine Malignant Tumors, *J Vet Intern Med*. 2004;18:219-222

Medical records of dogs with mammary carcinoma presenting to the University of Wisconsin-Madison were reviewed. Paclitaxel was administered to three dogs with histologically confirmed malignant mammary carcinomas at a dose of 165 mg/m^2 BSA administered intravenously over 3-6 hours every three weeks. Two of these three dogs had a partial response with treatment: one dog had a progression free survival period of 84 days (four cycles of paclitaxel), and the second dog had a progression free survival period of 258 days (six cycles of paclitaxel).

b. Study Title: A Clinical Pilot Study to Examine the Safety of Paclical [PACCAL VET-CA1] in Metastatic Solid Tumour in the Dog. Study Number OAS-0501-CA.

A single group, single-center, open label dose escalation clinical study in 32 dogs with solid tumors was conducted to assess the safety and pharmacokinetics of PACCAL VET-CA1. Seven of the 32 dogs had advanced-stage mammary carcinoma. All seven dogs were intact females. Enrolled dogs were of any age, sex, or breed. Dogs were excluded from the study if they had been treated with systemic glucocorticoids within two months prior to study enrollment; had previously received chemotherapy, radiation therapy, hormonal, or other anti-neoplastic therapy; were pregnant or lactating; had a life expectancy of less than one month; had an active infection; had a clinically significant abnormality in vital organ function; or had a global activity score of ≥ 3 (score of 0 is normal, score of 3 = spontaneous tiredness or dyspnea [without exertion], often lies on the floor).

PACCAL VET-CA1 was administered as an intravenous infusion at 5 mL/minute, every 21 days for up to three cycles. The initial dose ranged from 100 to 150 mg/m^2. Dose reductions or delays were permitted to manage adverse reactions. Two of the seven mammary carcinoma dogs had dose reductions.

Variables Measured: Response outcome (change in tumor size according to World Health Organization [WHO] criteria) was categorized relative to baseline measurements as complete response (CR, 100% disappearance of all lesions), partial response (PR, ≥ 50% decrease), progressive disease

(PD, ≥ 25% increase), and stable disease (SD, any change that was not CR, PR, or PD). Progression free survival (PFS) was defined as the time from first treatment to the first observation of disease progression or death from any cause.

Results: Four of seven dogs with mammary carcinoma had a CR or PR as the best overall response (best response at any time during the study). Three of seven dogs with mammary carcinoma had CR or PR at the study end (Days 77-84). PFS for the dog with CR was one year and survival was 498 days. Of the two dogs with PR, one had subsequent surgical excision of the tumor resulting in long term control and survival of 480 days. The other dog with a PR at study end had PFS and survival of 131 days. The dogs that had progressive disease at study end had PFS of 20-56 days and survival of 40-56 days.

A summary of the results of the 10 dogs with mammary carcinoma treated with paclitaxel in the two studies are presented in Table 1 below.

Table 1: Summary of Results of 10 Dogs With Mammary Carcinoma Treated With Paclitaxel.

Study	Tumor Histology	Best Overall Response[a]	Response at Study End	PFS (days)	Survival (days)
OAS-0501-CA	Carcinoma simplex	CR	CR	1 yr[b]	498[c]
OAS-0501-CA	Squamous cell carcinoma (mammary gland)	PR	PR	67[d] (1 yr[b])	480
OAS-0501-CA	Anaplastic carcinoma simplex	PR	PR	131	131
OAS-0501-CA	Adenocarcinoma	PR	PD	56	56
OAS-0501-CA	Adenocarcinoma	PD	PD	42	42
OAS-0501-CA	Carcinoma simplex	PD	PD	20	41
OAS-0501-CA	Carcinoma simplex	PD	PD	40	40
Poirier et al.	Adenocarcinoma	PR	PD	258	439
Poirier et al.	Adenocarcinoma	PD	PD	43	240
Poirier et al.	Adenocarcinoma	PR	PD	84	164

[a] Best response that occurred at any time during the study
[b] End of study follow-up was at 1 year, therefore censored from this point
[c] Small mass noted along mammary chain 1 week after study end and another noted 1 week prior to 6-month follow up. Mass that appeared 1 week after study end did not progress at time of 6-month follow up. Did not meet WHO criteria for stage III, IV or V disease.
[d] Paclitaxel reduced tumor size and allowed for surgical resection, therefore local progression was censored at this point.

Collectively, 6 of the 10 dogs with mammary carcinoma that were treated with paclitaxel were assessed as responders (CR or PR), including three dogs with PFS greater than four months, and one additional dog whose response to

paclitaxel allowed subsequent surgical excision of the tumor resulting in long term control.

2. Squamous Cell Carcinoma

Reasonable expectation of effectiveness for the treatment of resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy is supported by clinical data from 17 dogs in two pilot studies with oral and non-oral squamous cell carcinoma (some with metastatic disease) that received treatment with paclitaxel as an intravenous infusion every three weeks for up to four treatments.

a. Study Title: "An exploratory study on the efficacy of Paccal Vet in dogs with squamous cell carcinoma", Study Number OAS-11-SCC-01

A single group, multi-center, open label study in 14 dogs with squamous cell carcinoma was conducted to assess the efficacy and safety of PACCAL VET-CA1. Dogs of any age, weight, breed or sex, with a life expectancy of more than one month, clinically measurable disease with a longest diameter of ≥ 20 mm, and normal neutrophil and platelet counts at inclusion. Dogs were excluded from the study if they had a concurrent condition requiring treatment with systemic glucocorticoids, had gastrointestinal symptoms of VCOG-CTCAE grade > 2, had an active infection, or were pregnant or lactating. Ten male and four female dogs were enrolled. Lesion locations included oral/tonsil, prepuce, nose/nares, and extremity. Four dogs had metastatic disease. One dog had previously received chemotherapy, one dog previously received radiotherapy, and one dog had previous surgery for treatment of the squamous cell carcinoma.

PACCAL VET-CA1 was administered at an initial dose of 150 mg/m^2 BSA intravenously over 15-30 minutes. Dose reductions of 25 mg/m^2 or dose delays of up to 14 days could be used to manage adverse reactions. Two dogs had dose reductions and one dog had a dose delay during the study.

Variables Measured: Response to treatment was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) where response is measured relative to baseline measurements of the longest diameter of the tumor(s): complete response (CR, disappearance of all lesions), partial response (PR, ≥ 30% decrease in the sum of the longest diameter of target lesions), progressive disease (PD, ≥ 20% increase in the sum of the longest diameter of target lesions or appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions), or stable disease (SD, does not meet criteria for CR, PR or PD).

Results: Response to treatment was evaluated by tumor measurements prior to each treatment cycle. Dogs were evaluated for the best response at any time during the study, response at study end, and progression free survival (PFS). One dog died prior to the first tumor response measurement (Day 8), and three dogs were lost to follow up during the study. The two dogs with SD that were maintained through study end (Day 84) had PFS of 91 and 144 days (censored to last contact). PFS

ranged from 21-63 days for dogs that developed progressive disease (n=8) before study end.

Safety: The most common adverse reactions were neutropenia, vomiting, diarrhea, decreased appetite or anorexia, and dehydration. One dog died secondary to aspiration pneumonia and sepsis, even though supportive care was administered. The adverse reaction profile was similar to that reported in the multi-dose laboratory safety study and a clinical field study (see Target Animal Safety).

b. Study Title: A Clinical Pilot Study to Examine the Safety of Paclical [PACCAL VET-CA1] in Metastatic Solid Tumour in the Dog. Study Number OAS-0501-CA.

A single group, single-center, open label dose escalation clinical study in 32 dogs with solid tumors was conducted to assess the safety and pharmacokinetics of PACCAL VET-CA1. Three of the 32 dogs had oral squamous cell carcinoma. Enrolled dogs were of any age, sex, or breed. Dogs were excluded from the study if they had been treated with systemic glucocorticoids within two months prior to study enrollment; had previously received chemotherapy, radiation therapy, hormonal, or other anti-neoplastic therapy; were pregnant or lactating; had a life expectancy of less than one month; had an active infection; had a clinically significant abnormality in vital organ function; or had a global activity score of ≥ 3 (score of 0 = normal; score of 3 = spontaneous tiredness or dyspnea without exertion, often lies on the floor).

Variables Measured: Response outcome (change in tumor size according to World Health Organization [WHO] criteria) was categorized relative to baseline measurements of the longest diameter of the tumor as complete response (CR, 100% disappearance of all lesions), partial response (PR, ≥ 50% decrease), progressive disease (PD, ≥ 25% increase), or stable disease (SD, any change that was not CR, PR, or PD). Progression free survival (PFS) was defined as the time from first treatment to the first observation of disease progression or death from any cause.

Results: Of the three dogs with squamous cell carcinoma, one had a CR, one had a PR, and one had PD at the study end (Day 84). The dog with PR at study end had a PFS of 260 days, and the dog with CR at study end had not progressed at 388 days.

Safety: Adverse reactions that occurred in the three dogs with squamous cell carcinoma were fatigue, vomiting, diarrhea, anorexia, neutropenia, leukopenia, thrombocytopenia, pyrexia, weight loss, dehydration, and alopecia. One dog had dose reductions at cycles 2 and 3 to manage severe diarrhea. The adverse reaction profile was similar to that reported in the multi-dose laboratory safety study and a clinical field study (see Target Animal Safety).

A summary of the results of the 17 dogs with squamous cell carcinoma treated with paclitaxel in two pilot studies are presented in Table 2 below.

Table 2: Summary of Results of 17 Dogs With Squamous Cell Carcinoma Treated With Paclitaxel.

Study	Tumor Location	Best Response[a]	Response at Study End (Day 84)	PFS (days)
OAS-0501-CA	Oral	CR	CR	388[b]
OAS-0501-CA	Oral	PR	PR	260
OAS-0501-CA	Oral	PR	PD	64
OAS-11-SCC-01	Left metacarpus	SD	SD	144[b]
OAS-11-SCC-01	Right cervical LN[c]	SD	SD	91[b]
OAS-11-SCC-01	Submandibular LN[c]	PR	Withdrawn reason unknown	77
OAS-11-SCC-01	Oral	PR	PD	63
OAS-11-SCC-01	Prepuce	SD	Withdrawn for PD	63
OAS-11-SCC-01	Prepuce	SD	Lost to follow up	61
OAS-11-SCC-01	Submandibular	SD	Withdrawn for PD	54
OAS-11-SCC-01	Nares	SD	Withdrawn for PD	53
OAS-11-SCC-01	Oral cavity	PD	Withdrawn for PD	42
OAS-11-SCC-01	Prepuce	SD	PD	42
OAS-11-SCC-01	Nose	SD	Withdrawn reason unknown	42
OAS-11-SCC-01	Nasal planum	PD	Withdrawn for PD	21
OAS-11-SCC-01	Oral	PD	Withdrawn for PD	21
OAS-11-SCC-01	Right tonsil	n/a[d]	n/a	8

[a] Best response that occurred at any time during the study
[b] Censored to last contact when dog was alive without progression.
[c] Primary tonsillar lesion, lymph node was target lesion.
[d] This dog died at Day 8, prior to any tumor measurement

Collectively, two of the 17 dogs with squamous cell carcinoma that were treated with PACCAL VET-CA1 were assessed as responders (CR or PR), and two dogs had stable disease (SD) that was maintained through study end (Day 84). The dog with CR at study end had a PFS of 388 days (censored to last contact) and the dog with PR at study end had PFS of 260 days. The SD may represent a clinically relevant response, and dogs with SD had PFS of 91 and 144 days (censored to last contact). PFS ranged from 21-64 days for dogs that developed PD (n=9) during the study.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study

1. Study Title and Number: Pivotal Target Animal Safety Study of PACCAL-VET (Paclitaxel) in Dogs, Study Number KFI-046-SC-1109

2. Type of Study: Laboratory Study

3. Study Dates: July 13, 2009 – December 22, 2009

4. Location and Investigator:

   Kingfisher International, Inc.
   Ontario, Canada

5. General Design

   Purpose of Study: The purpose of this study was to demonstrate the safety of paclitaxel administered intravenously once every three weeks to dogs at 0, 130, and 150 mg/m^2 BSA for four doses.

   Description of Test Animals: Twenty-four dogs (12 males, 12 females) were enrolled in the study. Study dogs were approximately 6 to 13 months old and weighed 11.6 to 19.7 kg (25.5 to 43.3 lbs.) at the first treatment. All dogs were healthy based on physical examination, hematology, chemistry, urinalysis, fecal examination, and coagulation times.

   Control and Treatment Groups:

   Table 3: Control and Treatment Groups

Tx Group	Dose	Number and Sex of Animals
T0	Lactated Ringer's Solution	4 males 4 females
T1	Paclitaxel 130 mg/m^2	4 males 4 females
T2	Paclitaxel 150 mg/m^2	4 males 4 females

   Randomization: Prior to the first dose, dogs were randomized within gender to one of three groups without regard to body weight. Within each cohort, dogs were randomized to pens without regard to sex or treatment. All randomization was conducted using the PLAN procedure in SAS (SAS Institute, Cary, North Carolina).

   Drug Administration: The Lactated Ringer's Solution (LRS) or paclitaxel was administered through an intravenous catheter placed in the cephalic vein. Catheter placement was alternated between the left and right cephalic veins for consecutive treatments. Once reconstituted, the total paclitaxel dose or

LRS was administered over approximately 30 minutes. Dogs in group T0 were administered a volume of LRS equal to the volume administered to dogs in group T2 of the same weight.

Variables Measured: Physical examination, neurologic examination, body weight, food consumption, heart rate, respiratory rate, body temperature, behavior, injection site observations, complete blood count, serum chemistry, coagulation profile, urinalysis, fecal consistency and character, electrocardiogram and paclitaxel plasma concentrations.

Statistical Methods: The unit of observation and statistical analysis was the individual dog. For continuous outcomes measured only once during the study (organ weights), ANOVA was used to evaluate a model containing treatment, sex, and the sex-by treatment interaction as fixed effects. Where appropriate, pair-wise comparisons of each treatment group against placebo was made using linear contrasts at an unadjusted alpha = 0.10.

Continuous variables measured at multiple times during the study were analyzed by a repeated measures analysis of covariance, with treatment, sex, day, treatment by sex, sex by day, treatment by day, and treatment by sex by day terms in the model as fixed effects, and animal identified as the subject in the repeated statement. For variables measured at equal intervals, the covariance structure in the repeated measures analysis was investigated using four structural assumptions, namely, compound symmetry (CS), CS heterogeneous (CSH), first order autoregressive [AR(1)], and heterogeneous first order autoregressive [ARH(1)]. For variables measured at unequal intervals, the covariance structure in the repeated measures analysis was investigated using three structural assumptions, namely CS, CSH and spatial power [SP(POW)]. For each variable, the assumption giving the minimum value of the Akaike's Information Criterion (AIC) was selected in the final analysis. Where appropriate, pair-wise comparisons of each treatment group against placebo were made using linear contrasts at an unadjusted alpha = 0.10.

6. Results

No dogs died, or required euthanasia or removal from the study prior to the end of the study. Several dogs did require supportive care (intravenous fluids, antibiotics, anti-emetics, gastrointestinal protectants) to manage paclitaxel related toxicities. Where applicable, study findings were evaluated using the Veterinary Cooperative Oncology Group - common terminology criteria for adverse events(VCOG-CTCAE).

a. Clinical Observations and General Health Observations: Paclitaxel group dogs had increased frequency of diarrhea for 3-4 days following treatment, and increased frequency of hematochezia throughout the study. Two paclitaxel group dogs had melena at one observation. Dogs in all groups had abnormal feces at some point during the study.

During the study paclitaxel group dogs had a higher frequency of vomiting compared to the control group dogs. There were two occurrences of vomiting within 8 hours after treatment with 150 mg/m^2 paclitaxel. Post-treatment vomiting usually occurred within four days of paclitaxel administration.

Neurologic examinations were normal for all dogs during the study.

Mean heart rates were higher in the paclitaxel group dogs compared to the control group dogs during the first 8 hours after treatment and for all clinical observations during the study. This finding is not considered clinically relevant because there was less than a 10 bpm mean difference between the paclitaxel groups and the control group.

Injection site swelling occurred twice as frequently in the paclitaxel groups compared to the control group. Swelling was noted as early as 1 hour after treatment, but occurred most commonly 4-8 hours after treatment. All occurrences of injection site swelling resolved within one day.

Dermal changes were noted in paclitaxel group dogs starting on Day 42. Subcutaneous masses were noted in two dogs from each paclitaxel group, and ulceration or scabbing was noted in three dogs from each paclitaxel group. Whisker loss and facial alopecia affected seven 130 mg/m^2 group dogs and all 150 mg/m^2 group dogs, and coat thinning affected three 130 mg/m^2 paclitaxel group dogs and seven 150 mg/m^2 paclitaxel group dogs.

b. Electrocardiograms (ECG): There was no treatment effect on ECG tracings and cardiac conduction during the study.

c. Body Weight: Paclitaxel group dogs had decreased body weight in the first week following paclitaxel administration with a rebound in weight during the second and third weeks.

d. Food Consumption: Paclitaxel group dogs had a 20-100% decrease in food consumption on administration days and for 1-3 days after paclitaxel administration.

e. Clinical Pathology

Hematology
Hematology was collected seven days after the first three treatments and daily after the last treatment. Findings after the last treatment demonstrated that the nadir for hematology variables occurs one to four days after paclitaxel administration . Therefore changes in hematology were not completely captured following the first three administrations. Paclitaxel related changes included leukopenia, neutropenia (VCOG-CTCAE grades 1 – 3), lymphopenia, monocytopenia, anemia (VCOG-CTCAE grade 1), decreases in hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular volume (MCV), and thrombocytopenia (VCOG-CTCAE grade 1-2). Return to normal values was observed within three weeks.

Serum Chemistry
There were statistically significant differences for the paclitaxel groups compared to the control group for the albumin:globulin ratio, aspartate aminotransferase (AST), albumin, creatine kinase (CK), calcium, chloride, cholesterol, lactate dehydrogenase (LDH), and unconjugated bilirubin. Not all of these were considered clinically or toxicologically relevant.

Albumin: On Days 7, 27, 42, and 48 the mean albumin was significantly lower ($p<0.10$) in one or both paclitaxel groups compared to the control group. No control group dogs had albumin values below the reference range, while paclitaxel group dogs frequently had values near or below the lower end of the reference range. The decreased or low albumin values in paclitaxel group dogs were most likely secondary to gastrointestinal inflammation.

Alkaline Phosphatase (ALP): There were no statistically significant changes in ALP between the paclitaxel and control groups. Three dogs in each paclitaxel group had an increase in ALP following treatment one or more times during the study.

Alanine Aminotransferase (ALT): There were no statistically significant changes in ALT between the paclitaxel and control groups. One 130 mg/m^2 group dog had a VCOG-CTCAE grade 1 toxicity on Day 67, and three 150 mg/m^2 group dogs had VCOG-CTCAE grades 2-3 toxicity between Days 27-67.

Total Bilirubin: One male dog from each paclitaxel group had single elevations in total bilirubin on Day 27 or 48. These changes were not associated with clinical signs.

Creatine Kinase (CK): On Days 21, 27, 63, and 67 the mean CK was significantly higher ($p<0.10$) in one or both paclitaxel groups compared to the control group.

Urinalysis: There were no statistically significant, clinically relevant, or toxicologically relevant changes in urinalysis variables.

Coagulation Profile: There were no treatment related differences for prothrombin time (PT) and partial thromboplastin time (PTT). The mean fibrinogen was significantly higher ($p<0.10$) in the paclitaxel groups compared to the control group on Days 7, 27, 48, and 67, and lower on Days 0 and 21. Mean fibrinogen remained within the normal range for the paclitaxel and control groups, while individual dogs in the paclitaxel groups had elevated fibrinogen on some days.

Buccal Mucosal Bleeding Time (BMBT): There was no treatment effect on BMBT, even when measurement occurred concurrently with thrombocytopenia.

f. Pharmacokinetics: Toxicokinetic data confirmed that there was no clinically relevant accumulation that occurred when paclitaxel was administered once every three weeks by intravenous infusion at a dose of 130 to 150 mg/m^2. Paclitaxel concentrations achieved with the 130 mg/m^2 dose are directly proportional to that which was achieved with the 150 mg/m^2 dose.

g. Pathology: There were no clinically relevant changes in the control group dogs on gross necropsy and histopathology. One control group dog had changes at the site of catheter placement and one had hypercellular bone marrow. The bone marrow changes may have been a response to the daily blood collections for clinical pathology following the last treatment.

Treatment related necropsy findings in the 130 mg/m^2 paclitaxel group included whisker loss (n=6), alopecia (n=5), injection site hemorrhage (n=1), and subcutaneous mass with dermal ulceration (n=1). One 130 mg/m^2 paclitaxel group dog did not have any abnormalities on necropsy. Treatment related necropsy findings in the 150 mg/m^2 paclitaxel group included whisker loss (n=8), alopecia (n=7), healing wound (n=3), focal/ulcerative dermatitis (n=2), and subcutaneous mass (n=2).

Histopathology findings related to LRS administration in the control group included injection site inflammation and hypercellular bone marrow (n=1 each). Histopathology findings in the 130 mg/m^2 paclitaxel group included injection site inflammation and thrombosis (n=4), extramedullary splenic hematopoiesis (n=7), and hypercellular bone marrow (n=2). Histopathology findings in the 150 mg/m^2 paclitaxel group included mild mineralization and smooth muscle hypertrophy in the media of the aorta (n=1), oligospermia (n=1), injection site inflammation and thrombosis (n=4), extramedullary splenic hematopoiesis (n=8), and hypercellular bone marrow (n=1). On histopathology regenerative hair follicles were noted in paclitaxel group dogs, suggesting the alopecia may not be permanent.

7. Conclusion: Paclitaxel administered at 130 mg/m2 or 150 mg/m2 has a narrow margin of safety. All dogs that received paclitaxel experienced related toxicities during the study. Dogs that required supportive care for neutropenia, vomiting, or diarrhea responded appropriately and were able to continue and complete the study. Injection site swelling indicates that paclitaxel is a vascular irritant when administered through an intravenous catheter over 30 minutes. All occurrences of injection site swelling resolved within one day. Subcutaneous injection of other medications may result in local fat necrosis and inflammation while the patient is treated with paclitaxel.

B. Clinical Field Study

Study Summary
In a 14-week masked, controlled clinical field study, 168 dogs were randomized to receive treatment with paclitaxel. Enrolled dogs had nonresectable Grade II or III (stage 2a or 3a) cutaneous mast cell tumors without metastases, were 1 to 14 years old (mean age 9 yrs.), and weighed 11 to 154 lbs. (mean 62 lbs.) on the first day of the study. Dogs were treated with paclitaxel at 150 mg/m^2 every

three weeks for four cycles, with dose reductions or delays to manage adverse reactions. Data were not sufficient to demonstrate substantial evidence of effectiveness.

Adverse Reactions
All dogs experienced adverse reactions. Eleven dogs discontinued treatment, 5 dogs died, and 3 dogs were euthanized due to adverse reactions during the study. The most common adverse reactions noted during the study, in decreasing frequency, were: neutropenia, vomiting, anorexia, diarrhea, lethargy, alopecia, dehydration, dermatitis, hepatopathy, fever, edema, lameness, urinalysis abnormalities, pruritus, erythema, anemia, loss of body condition or weight loss, cutaneous ulceration, thrombocytopenia, neoplasia, polydipsia, and conjunctivitis.

Table 4. Common Adverse Reactions in Paclitaxel Treated Dogs (n=168)

Adverse Reaction	Number affected	Percent affected
Neutropenia	137	82%
Vomiting	133	79%
Anorexia	127	76%
Diarrhea	118[a]	70%
Lethargy	116	69%
Alopecia	66	39%
Dehydration	43	26%
Dermatitis	40[b]	24%
Hepatopathy	32[c]	19%
Edema	24	14%
Pyrexia	22	13%
Lameness	20	12%
Urine abnormality	16	10%
Pruritus	16	10%
Erythema	14	8%
Anemia	13	8%
Loss of body condition	12	7%
Ulceration, cutaneous	12	7%
Thrombocytopenia	11	7%
Neoplasia	11	7%
Polydipsia	10	6%
Conjunctivitis	10	6%
Death	5[d]	3%
Euthanasia	3[d]	2%

[a] Nine dogs had hemorrhagic diarrhea

[b] Eight dogs had pyoderma and eleven had undefined skin lesions
[c] One dog had hepatomegaly
[d] Not related to disease progression

Adverse reactions that occurred in less than 6% of dogs during the study included leukopenia, lymphopenia, hypoproteinemia, hypoalbuminemia, hypotension, colitis, melena, hematochezia, septicemia, injection site reactions, transient aggression, behavioral changes, shivering, heart murmur, weakness, benign tumors, abdominal pain, dyspnea, decreased appetite, gastrointestinal ulceration, panting, tachycardia, mast cell tumor degranulation, acute tumor lysis syndromes, and possible cerebrovascular event.

Conclusion
Paclitaxel had a low margin of safety in this study. Adverse reactions were common but manageable by monitoring patients regularly, using dose reductions or dose delays, or by providing supportive care (intravenous fluids, antibiotics, anti-emetics, gastrointestinal protectants).

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for the conditional approval for this application for conditional approval.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PACCAL VET-CA1:

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Persons sensitive to retinoids should avoid contact with PACCAL VET-CA1.

Paclitaxel is cytotoxic and can cause birth defects and affect female and male fertility. Wear protective gloves to prevent contact with feces, urine, vomit and saliva for three days after the dog has received treatment. Place all waste material in a plastic bag and seal before disposal. Pregnant and breast feeding women should not prepare or administer the product.

Special instructions for preparing and administering the product:

- PACCAL VET-CA1 should be administered under the supervision of a veterinarian experienced in the use of cancer chemotherapeutic agents.
- Use standard measures for the safe handling of cytotoxic drugs.
- Wear gloves, goggles and protective clothing.
- Do not eat, drink or smoke while handling the product.
- Do not store food in or near the preparation area.

Accidental skin contact

- In case of accidental contact with the skin, wash the affected area immediately and thoroughly with soap and water.

Accidental eye exposure

- Remove contact lenses.
- Rinse the eyes with large amounts of tap water (use eyewash station if present) for at least 10 minutes while holding back the eyelid.
- Seek medical advice immediately and show the package insert or label to the physician.

Accidental self-injection

- Remove glove
- Let the wound bleed a few drops of blood.
- Rinse the wound thoroughly with plenty of tap water.
- Seek medical advice immediately and show the package insert or label to the physician.

On the Client Information Sheet:

How do I care for my dog after it is treated with Paccal Vet-CA1?

• Because Paccal Vet-CA1 is a cancer treatment drug, extra care must be taken when handling and cleaning up after your dog for three days after treatment with Paccal Vet-CA1.

• Cleaning up after your dog:

––Avoid direct contact with urine, stool, vomit and saliva for three days after your dog is treated with Paccal Vet-CA1.

––When cleaning up urine, stool, vomit or saliva you should wear disposable gloves and collect the contaminated material with disposable absorptive material (such as paper towels) and place them into a plastic bag. Carefully remove the gloves and place them in the bag and tie or fasten it securely. Wash your hands thoroughly afterwards.

––You should not wash any items accidently soiled with urine, stool, vomit or saliva from your dog with other laundry for three days after treatment.

––Do not let your dog urinate or defecate in areas where people may come in direct contact with the urine or stool.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that PACCAL VET-CA1, when used according to the label, is safe and has a reasonable

expectation of effectiveness for the treatment of nonresectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy, and for the treatment of resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy.

A. Marketing Status:

PACCAL VET-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose mammary carcinoma and squamous cell carcinoma, and to monitor safe use of the product, including treatment of any adverse reactions.

B. Exclusivity:

PACCAL VET-CA1, as approved in our approval letter, qualifies for SEVEN years exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it is a designated new animal drug under section 573(a) of the act. Except as provided in section 573(c)(2) of the act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as PACCAL VET-CA1 until after expiration of the exclusive marketing rights. Because this is the first time we are approving this active ingredient in a new animal drug, this drug also qualifies for five years of exclusivity under section 512(c)(2)(F)(i) of the act. The exclusive marketing rights and exclusivity for this drug run concurrently.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.